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ORGANIZATION OF A LARGE-SCALE CORTICAL NETWORK

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SUMMARY

This research program has been directed at discovering neurobiological features (cell specializations, activity patterns in collections of neurons, circuit design features) essential to the encoding, organizing, and utilizing recognition memories by networks in mammalian cortex. Three levels of work have been involved: 1) physiological and anatomical analyses of specific, well defined examples of telencephalic networks; 2) translation of the neurobiological results into computer simulations of the networks; 3) testing of the physiological and behavioral predictions of the computer models. It is anticipated that the results of the research will provide the bases of formal hypotheses regarding the links between cortical properties and computational operations and provide guidelines for the design of novel devices capable of dealing with the difficult computational problems presented by real world environments. The following points summarize the progress made towards these goals during the tenure of ONR Grant #N00014-86-K-0333.

(1) Links were discovered between learning related brain rhythms and the cellular machinery that causes stable changes in synaptic strength. These relationships were converted into a set of biologically valid, synaptic "learning rules" for implementation in neural networks. These rules describe where and when changes will occur on cells receiving complex spatio-temporal patterns of input activity. The observation that rhythmic activity has a profound impact on the operations of cortical networks directly influenced nearly all aspects of the modelling efforts that followed.

(2) The above discoveries were made in hippocampus, a structure in many ways ideal for neurobiological work but less than appropriate as a starting point for building computer simulations with predictive power (see original proposal for arguments relating

to this point). The olfactory bulb-olfactory (piriform) cortex was selected as a target for modelling and it was essential to establish that the rules developed for hippocampus extend to this system. Experimental work showed that the basic cell biology and spatio-temporal patterns involved in modifying hippocampus held true for cortex as well. Differences are present and the origins and significance of these are still under study. A particularly noteworthy point established by the neurobiological work is that the basic sampling rhythm for olfaction (4-7 Hz) is uniquely effective in changing synaptic strength; this provides a connection between behavior and specific cellular phenomena.

(3) Two further tests were made of the behavioral significance of the phenomena and rules obtained from the neurobiological studies. First, the same rhythmic patterns of stimulation used to probe the networks *in vitro* were employed as discriminative cues in an olfactory learning problem. Rats learned and remembered these "electric odors" about as well as they did natural odors. Moreover, the same synaptic changes found in the *in vitro* experiments developed in the freely moving animals as learning occurred. Studies are still in progress on these phenomena. Second, drugs that block the neurobiological mechanisms that produce synaptic modifications also block learning, and do so without impairing recall. These results give us confidence that the biological properties we have identified are in fact critical to the formation of recognition memories.

(4) Computer simulations of the bulb-cortex system have been found to possess unexpected capacities for analyzing input stimuli and for organizing memories. Following learning of many cues, the model is able to recognize a complex (known) signal even when it is masked by a much stronger input. It does this by exploiting repetitive sampling and various inhibitory processes (simulations of inhibitory potentials found in cortical networks) it contains. Perhaps more remarkably, the simulation also builds perceptual hierarchies without outside supervision. As noted, the model uses repetitive sampling. In our earlier studies, we found that after extensive learning the model would generate a single response pattern (i.e., collection of cortical cells becoming active) to closely related signals in the stimulus world; responses on subsequent sample cycles were

unique to the cue now present. Recently, we have found that the combined bulb-cortex network will perform true hierarchical clustering in that it will form representations for groups, subgroups, and individuals. This is a task that is computationally difficult and one of considerable practical significance. We have extracted an alogrithm from a simplified version of the network and found it to be novel, parallel, and to show temporal linearity with regard to the number of network elements and input signals. Thus the model may be appropriate for silicon implementation and will scale upwards with linear cost. We are currently exploring engineering possibilities.

(5) The first tests of the predictions of the model have been carried out using chronic recording from the olfactory cortex of rats engaged in learning an odor discrimination problem. These experiments have confirmed that the cortex uses sparse coding (i.e., few cells respond to any given odor) and that its activity is synchronized with the sampling rate. This work is still in progress and more detailed tests should be available shortly.

1. <u>Physiological studies of synaptic learning rules.</u>

Hippocampal long term potentiation serves as a model synaptic plasticity mechanism for rapid acquisition and long-term retention of memories for "facts" or "data". Our studies have aimed at identifying naturally-occurring cell discharge pattens that induce LTP and uncovering the cellular mechanisms responsible for the efficacy of these patterns. The hippocampal EEG during learning exhibits a sinusoidal 4-7 Hz EEG wave (theta) with short bursts of cell discharges rising on the peaks of the waves. Our prior work established that brief bursts of afferent stimulation, synchronized to the frequency of the theta rhythm (5 Hz) are optimal for induction of LTP in field CA1. We have now shown that this "theta burst" pattern is particularly effective because, by reducing synaptic inhibition, it promotes levels of postsynaptic depolarization sufficient to allow calcium influx through NMDA receptor-linked channels (Larson and Lynch, 1988). The voltage dependence of LTP induction proves to be a significant parameter in the operation of the piriform model (see below). Our prior work indicated that a burst of

activity in one input to a postsynaptic target cell does not induce LTP but "primes" the cell so that a burst to a separate input one theta cycle later does induce LTP. This provides one temporal rule for synaptic interactions and LTP. We have extended these studies to examine interactions between inputs within one theta cycle. A "primed" cell received asynchronous bursts to three separate inputs such that stimulation of the second input temporally overlapped stimulation of the first and third but the first and third did not overlap with each other. Most LTP was induced at synapses activated by the first burst, less by the second, and least by the third. This effect involves both retrograde facilitation and anterograde suppression effects within one theta cycle (Larson and Lynch, 1989; Greenberg *et al.*, 1988). Indeed, it appears that induction of LTP at one set of synapses is followed by a brief refractory period when LTP at other synapses is inhibited (Greenberg *et al.*, 1988). In summary, this set of studies accomplished two objectives. One, it identified for the first time a link between brain wave patterns and mechanisms that produce synaptic changes. Two, it provided a set of biologically valid synaptic learning rules for computer modelling.

Chronic recording techniques have been used to address two questions related to the stability of LTP. In the first, we simply asked how long the potentiation effect lasts. Rats were chronically implanted with stimulation electrodes in the Schaffer-commissural system and recording electrodes in the CA1 field. Responses were tested for several days before and 1-4 weeks after induction of LTP by theta burst stimulation (TBS). Once induced, LTP was found to persist in non-decremental fashion for as long as recording conditions could be maintained; in some cases this was several weeks (Staubli and Lynch, 1987). Given that LTP appears to persist indefinitely, the question arises as to whether or not particular patterns of synaptic activity might actively reverse it. LTP was induced by theta burst stimulation in the chronic preparation and shortly thereafter (5-10 min) the potentiated input was stimulated at low frequency (1-5Hz for 50-100 sec). In the majority of animals (64%) low frequency stimulation reversed the LTP when the animals were tested either 1 hr or 1 day later. Subsequent burst stimulation established that LTP could

be reinstated in these animals. Low frequency stimulation did not reduce responses on inputs that had not been potentiated (Staubli and Lynch, in press). These findings suggest that LTP can be persistent enough to encode long-term memories but may be subject to reversal shortly after its induction.

Ongoing studies are aimed at understanding the cellular basis of the theta-plasticity rules and the mechanism by which LTP can be reversed. In terms of building simulations, precise data concerning spatial and temporal interactions between synapses are crucial and these learning rules are being incorporated into current model.

2. **Piriform physiology, *in vitro.***

The synaptic learning rules developed thus far are based on the CA1 field of hippocampus. For a variety of reasons including more direct access to peripheral input, the model we are using for simulation work is of the piriform cortex. Therefore, we have been studying the basic physiology of this region with particular regard to plasticity mechanisms. Field potentials evoked in the superficial layers by stimulation of the lateral olfactory tract (LOT) or associational (ASSN) inputs to piriform cortex *in vitro* can be distinguished by three criteria: (1) visual placement of the stimulation electrode in either the LOT or in layer Ib, (2) laminar profile analysis, and (3) absence of paired-pulse facilitation at ASSN synapses.

Our first experiments were to establish the receptor pharmacology of these two systems and compare them to hippocampus. In the presence of physiological levels of extracellular magnesium, we found that the NMDA antagonist AP5 (50 uM), had no detectable effect on synaptic responses in either system but the non-NMDA antagonist DNQX (20 uM) completely suppressed responses in both systems. However, in magnesium-free medium both systems exhibited NMDA receptor-mediated responses as demonstrated either by the presence of a response in DNQX or the blockade of a response component in AP5 (Larson *et al.*, 1989).

For LTP experiments, two preparations were used. One of "rostral" piriform, containing the LOT and one of "caudal" piriform, beginning at the point where the LOT

ceases to be visible as a definable fiber tract. Theta burst stimulation to the LOT induced LTP in 16/48 slices examined, a proportion much lower than that observed in hippocampal experiments. Stimulation of ASSN inputs in rostral slices induced LTP in 16/30 cases but in 36/40 caudal slices. In both systems, TBS did not induce the immediate, decremental short-term potentiation observed in hippocampus, rather potentiation developed gradually over 1-2 minutes after TBS. The low success rate at LOT synapses raised the possibility that the NMDA system might be difficult to activate in these contacts. Stimulation with long 100 Hz trains was equally ineffective in slices that failed to potentiate after TBS; however, TBS applied in Mg^{++}-free medium, a condition which greatly facilitates NMDA receptor currents, induced LTP in 5/5 slices tested. The pharmacology of LTP induction was also studied in the caudal associational system where LTP induction was very reliable. Perfusion with AP5 blocked LTP induction in 9/9 slices and LTP was obtained after drug washout in 6/6 cases (Jung, Larson, and Lynch, in prep.).

These results indicate that both LOT and ASSN synapses in piriform cortex possess the NMDA receptor-linked LTP induction mechanism and that it can be activated by TBS. This encourages the speculation that the LTP rules derived from hippocampus hold for piriform as well, but demonstration of this requires further experiments.

3. Piriform synaptic plasticity *in vivo*.

Rats sample odors at the theta rhythm during mystacial sniffing and it is reasonable to assume that signals are processed by the olfactory system at this rhythm. Indeed, even the hippocampal EEG is synchronized to the sniff cycle. We have developed a paradigm to test learning-induced changes in synaptic efficacy in the piriform cortex using theta burst stimulation of the LOT as an "electric odor" discriminative stimulus. Rats were first trained on a two odor successive cue go-no go task for water reward. After learning-set acquisition, LOT stimulation was substituted for the positive odor. Single-pulses at the theta frequency did not elicit any obvious behavioral reaction, but when theta bursts were used most rats began sniffing and approached the water port as they do in response to

the positive odor. They rapidly learned to discriminate between the electric odor and real odors as well as between two separate electric odors. Examination of single-pulse responses evoked by the electrode used as a cue revealed a substantial synaptic potentiation (35%) after a single training session. This effect was still evident 24 hrs. later. Interestingly, the same stimulation pattern did not induce potentiation when given to naive animals, suggesting that some other system that facilitates synaptic plasticity is activated during learning sessions (Roman *et al.*, 1987). This may also relate to the difficulty in obtaining LTP in the LOT synapses in slices. In any case, bursts of activity occurring at the frequency of behavioral sniffing which is synchronized to the hippocampal EEG proves to be an effective sensory cue and, moreover, results in synaptic potentiation in piriform as in hippocampus. This provides a further link between the LTP-based learning rules derived from hippocampus and endogenous rhythms and behavior.

4. **Simulation and theoretical analysis of piriform cortex**

a) Hierarchical readout via repetitive sampling

Simulation and analysis of layer II of piriform cortex have incorporated a broad range of its anatomical and physiological characteristics in an attempt to understand how these properties might interact to produce coherent operation, and how these operations might generate recognizable, useful and testable computational and psychological function. Two networks, bulb and cortex, consisting of distinct architectures and physiologies, are extensively connected via both feedforward and feedback projections. The entire system works in synchrony with a 4-7 Hz (theta) sampling pattern that is characteristic of small mammals. Bulb mitral cells (these neurons innervated by the peripheral receptors and that project to cortex) receive inputs presented repetitively for brief periods. Inputs to the cortical network arise from the resultant synchronous bursting in a subset of mitral cells, yielding cyclic activity in relatively discrete "operation cycles" time-locked to the sampling rhythm. Sparse random connectivity in the simulation selectively activates those cortical cells whose dendrites are most connected to the input lines that are active.

Learning increments active synapses on sufficiently depolarized cells via an LTP rule. Input lines shared across many similar input cues, and thus participating in many learning episodes, will strengthen their target synapses more than lines which participate in relatively fewer episodes. The result is that cortical dendrites (which can be viewed as vectors being moved by synaptic learning) become increasingly well-tuned to those inputs containing the shared subset; i.e., those inputs that are sufficiently similar to constitute members of a cluster. We have shown that this circuit will generate cell-firing responses that group learned cues by similarity. That is, for a given threshold of input similarity among a set of cues, outputs are identical for all of the cues, whereas below that similarity threshold, outputs are much less similar than corresponding inputs (Granger, Ambros-Ingerson and Lynch, 1989). The predominantly feedforward collateral axons of the cortex enhance this effect (Granger, Whitson and Lynch, 1989).

Feedback from cortex to the bulb inhibitory layer in the model is trained via a correlational rule during an earlier "developmental" period. The feedback then selectively inhibits those bulb mitral cells that are most responsible for the cortical output response, via relatively long-lasting inhibition. Resulting renormalization of bulb activity produces a distinct spatial pattern of bulb mitral cell firing, which in turn activates a distinct set of cortical cells. This inhibitory feedback process can continue until bulb is sufficiently inhibited to be largely quiescent. Cortical responses after the initial (first sample) response become progressively more different for different cues, increasingly approaching unique encodings of individual cues.

Taken together, the resulting sequence of responses are hierarchically ordered such that the first-cycle response indicates similarity-based cluster information for learned cues whereas subsequent cycle responses denote increasingly subordinate categories (Granger, Ambros-Ingerson, Henry and Lynch, 1989; Granger, Ambros-Ingerson and Lynch, 1989). These findings suggest that sensory cues may be "iteratively recognized" at a sequence of successively lower levels, with the first level recognized corresponding to a natural "entry level" for perceptual processing. Cognitive studies of visual and conceptual recognition in

hierarchically organized domains indicate that such preferred recognition levels do exist and exert a strong influence over early processing: human subjects robustly prefer a "basic level" description (e.g., "bird" in the hierarchy animal-bird-sparrow), recognizing cues faster at this level and more frequently than either superordinate or subordinate referents for the same objects. We have found empirically that first-cycle responses from the piriform network robustly indicate the basic level as empirically identified in human experiments using the same hierarchically-organized data for both the human subjects and the simulation (Granger, Gluck, Crane and Lynch, 1989). The network first-cycle responses at the basic level are followed by subordinate level information in second and later cycles, separated by intervals of 200 msec simulated time in the model; interestingly, studies by Hoffmann and Ziessler (1983) indicate that average reaction time differences between recognition of the basic and immediately-subordinate description levels was 148 msec.

b) Information-theoretic view of hierarchical clustering

We have also found that a proposed mathematical predictor of the basic level effect successfully predicts both the human and network performance on this data (Gluck and Corter, 1985; Lynch, Granger, Larson and Baudry, 1989). This predictor is an information-theoretic measure of the information value of clustering of data into groups, measuring the increased information about features of a cue gained by knowledge of its category membership. Briefly, for cues considered as multidimensional vectors, if a particular cue dimension D can take on values $v_1 \ldots v_n$ with probabilities $p(v_1) \ldots p(v_n)$, respectively, then the uncertainty of the value of D is:

$$U(D) = -\sum_{i=1}^{n} p(v_i) \log p(v_i)$$

(Shannon 1948), and this uncertainty about the value of D for this cue can be reduced, via knowledge that the cue is in a particular category C, by the amount $U(D) - U(D/C)$ where

$$U(D|C) = -\sum_{i=1}^{n} p(v_i|C) \log p(v_i|C)$$

and $p(v_i/C)$ is the conditional probability of attribute value v_i given that the cue is in category C. Thus a measure of the overall information value I of a category is the

expected reduction in the uncertainty of the value of D due to knowledge of category membership:

$$\begin{aligned} I &= p(C)[U(D) - U(D|C)] \\ &= p(C)\left[-\sum_{i=1}^{n} p(v_i)\log p(v_i) - \left(-\sum_{i=1}^{n} p(v_i|C)\log p(v_i|C)\right)\right] \end{aligned}$$

The information-theoretic origin of the measure suggests that the clustering performed by the piriform network may be learning information-optimal clusters; this idea is being tested on a range of hierarchically-organized data by measuring the information value of the simulation-generated clusters and comparing them against optimal values (see Lynch, Granger, Larson, and Baudry (1989) for discussion), and analyzing sensitivity of these results to perturbations in parameters of the model.

A given cue population can be divided into clusters in factorially many ways (see Granger et al., 1988; Lynch, Granger, Larson & Baudry, 1989); Granger Ambros-Ingerson and Lynch (1989) empirically and analytically related synaptic parameters of the cortical simulation to its clustering performance, deriving a monotonic relation between the ratio of potentiated (maximum) to naive (minimum) synaptic weights, and the breadth (maximal distance between members) of the clusters formed from a given cue population. A developmental algorithm was proposed to sample the cue environment and set these weight parameters so as to automatically give rise to information-optimal clustering of the cues in the "adult" network (Granger, Ambros-Ingerson and Lynch, 1989).

c) LTP induction rules, layer III, and sequence learning

Simulation experiments have thus far focused primarily on the *expression* characteristics of LTP, embedded in a specific layer of cortex (layer II), emphasizing the sequential memory encoding and readout described. Initial experiments with the induction mechanisms of LTP indicate that the "sequence" rule described earlier, in combination with rules for the interaction of layer III cells and the basal dendrites of layer II and III cells, enables encodings that powerfully distinguish among cues consisting of slightly different sequences of cue constituents (e.g. ABC,BCA), which might occur given different

relative concentrations of chemicals, or different orders of frequencies or formant transitions occurring within a phoneme. In addition, modeling efforts aimed at the functional implications of a temporary, non-synapse-specific plasticity mechanism like that of potentiation of the dentate mossy fiber synapses on hippocampal CA3 pyramidal cells, and interactions between this short-term potentiation and long-term mechanisms (e.g., via via known feedback pathways from hippocampus to olfactory bulb), suggest that these mechanisms might combine to enable learning of longer temporal sequences of cues.

d) A novel algorithm for hierarchical clustering

The ability of the network to identify hierarchical statistical structure in data raises questions of characterization of the essential design features of the network underlying its hierarchical clustering ability. Analysis has recently led to such a characterization, and controlled testing revealed that the resulting simplified formation of the network provides a novel and efficient algorithm for hierarchical clustering.

The simplified formulation consists of a weight matrix W (corresponding to the layer I connectivity matrix; see Fig. 1) divided into H non-overlapping "winners-take-all" or "competitive" patches: sets P_1, P_2, ..., P_H of weight vectors C (i.e., columns of W) such that $W = U_i P_i$. The network is trained on a set of N-dimensional real-valued vectors (i.e., spatial patterns of activation in the lateral olfactory tract), via an extension of a correlational (Hebbian) learning algorithm (a simplification of the LTP rules for synaptic modification). For each input vector X, the column vectors (dendrites) C that win the (winners-take-all) competition on X (corresponding to target calls that are most depolarized by this input) are identified. The synaptic contacts on these vectors are then trained, moving the vectors closer to X by an increment γ_c. Feedback from the just-trained vectors then partially inhibits or 'masks' the input. The remainder of the input is presented to the next network patch matrix in the hierarchy, until all H hierarchical subnets have been trained, over H operation cycles. At any given hierarchical level, the Cs can be shown to converge to the means of the clusters of cues on which they are trained, as in related "competitive learning" algorithms (e.g., von der

Malsburg, 1973; Grossberg, 1976; Kohonen, 1984; Rumelhart and Zipser, 1986). The feedback inhibition step enables vectors in W assigned to the subordinate hierarchical levels to converge to means of subclusters of the data, allowing secondary (and H-ary) structure to be identified (for H divisions of the weight matrix).

Formally:

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for X in training-sample
    for h ∈ {1, 2 ..., H}
        for C ∈ win(X, P_h)
            C ← C + γ_c(X − C)
        end-for
        X ← X − mean(win(X, P_h))
    end-for
end-for                                        (1)
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where H is the depth of the hierarchy; C is the subset of weight vectors in a patch P_h that wins the competition on the input X; $\text{win}(X, P_h) = \{C \in P_h : X \cdot C = \max_{C_i \in P_h}(X \cdot C_i) \wedge X \cdot C > 0\}$; and γ_c is the learning rate.

Testing has shown that this novel network algorithm robustly identifies hierarchical statistical structure in data, and that its results compare well with those for standard hierarchical clustering techniques. Moreover, the algorithm is inherently efficient, and scales linearly with the size of the cue population to be clustered. In particular, the space complexity of the algorithm is $O(n)$, i.e., the number of nodes required for completion separation of n cues depends only linearly on n; and training time per presentation is also linear in the total number of categories of cues to be distinguished (Ambros-Ingerson, Granger and Lynch, 1989).

Simulation and theoretical analysis of this cortical network has thus provided an instance in which a novel and efficient algorithm for a well-studied computational problem has been developed from a specific cortical network. Reflecting the system from which it was derived, the algorithm is inherently parallel and hence lends itself to implementation in silicon. A collaborative effort with Dan Hammerstrom of Adaptive

Systems, Inc., is undertaking the design of a novel chip ("silicon cortex") based on the network analysis described here. Bailey and Hammerstrom (1988) have shown the need for multiplexing of interconnections in silicon implementations of networks of sizes on the order of hundreds of thousands of cells, via analysis of the space constraints involved in available CMOS processes, and have designed a novel technique (Augmented Broadcast Hierarchy) for this purpose, which is being used in the implementation of this cortical network.

5. Single-unit recording in piriform cortex in behaving rats.

Recordings of single-cell activity during olfactory behavior are used to test the validity of the model. Animals are trained in a two-odor successive cue go-no go olfactory discrimination task. After about 5 sessions using different odor pairs, the rats acquire a new discrimination within about five trials. Single-units in piriform are recorded using tungsten microelectrodes attached to a moveable microdrive implanted to the skull. Once a cell is isolated, the animal is run on several training sessions using novel or previously-learned odor pairs.

To date we have recorded activity in some 60 well-isolated units. On the basis of mean firing rate, these units fall into two obviously different categories. Type I units are the most commonly encountered (55/60), have rather slow discharge rates (1-5 Hz), broad spikes (>500 msec duration of negativity, filtered), and occasionally emit a high frequency burst of 2-12 spikes (100 Hz). Type II units are rare (5/60), fire rapidly (20-50 Hz), and have narrow spikes (<500 msec negativity).

Depending on how long the unit can be held, firing patterns are recorded during 2 to 20 sessions with different odor pairs. Over half (24/43) type I units did not respond to any of the odors tested, typically four sessions (8 odors). Eight units showed selective firing to only one of the odors tested. The rest responded with increased firing to more than one odor. The characteristic response of a sensitive unit consisted of a single spike or a short burst on the majority of trials when that odor was presented. The response typically occurred 250 msec after the valve was switched to present the odorant.

Some of the type II units we have thus far recorded have shown interesting properties. Activity of these rapidly firing cells shows a marked suppression (sometimes near complete silence after firing at 20-40 Hz) when the rat enters the sniff port (odor delivery area) but before odor onset. Upon odor presentation, the cells resume firing, sometimes beginning with a "rebound burst". Since we suspect these neurons to be inhibitory interneurons, this may indicate a suppression of inhibition while the animal is awaiting the olfactory cue. However, it is clear that we need to record many more of these cells to verify these conclusions.

Although these results are clearly preliminary, and more data is needed, it is clear that piriform units are not responding in global fashion to any odor presented. Over 75% of the type I cells tested responded to less than two of the array of odors presented. The anatomy and connectivity of piriform as well as the operation of the network model suggest sparse coding of odors and our preliminary results suggest this to be the case.

6. <u>Studies of olfactory behavior: LTP and memory.</u>

Behavioral studies are used to test predictions of the model and examine how higher-order effects can arise from the simpler functions achieved by the network. Results from the simulation suggest that the capacity of the olfactory memory system should be large and hence that representations for learned odors should not suffer interference from new learning and that mixtures of novel odors should be treated differently than mixtures of previously learned odors. Also of interest is how other brain networks, such as the dorsomedial nucleus and hippocampus interact with piriform in olfactory memory storage.

One key assumption we have made is that LTP is used as the learning mechanism for representational forms of memory. We have tested this by asking whether or not LTP and memory share a common pharmacology. That is, if LTP is involved in memory encoding, it is expected that drugs which disrupt LTP should also prevent acquisition of new representations. The NMDA receptor is a logical place to start since it is crucial to LTP induction and potent and selective antagonists for the receptor are available. We

had previously shown that intraventricular infusion of AP5 blocks LTP *in vivo* and also prevents acquisition of spatial representations (maps) required for navigation in a water maze (Morris *et al.*, Nature 319: 774-776, 1986); we have now tested the effects of this manipulation on olfactory discrimination learning. We used a two-odor simultaneous-presentation olfactory discrimination task. Rats were trained on 8 pairs of odors prior to AP5 treatment. After AP5, acquisition of new discriminations was impaired although memory for previously learned odors was intact (Staubli *et al.*, 1989).

We had also previously shown that intra-ventricular administration of leupeptin, a protease inhibitor, blocks both spatial (Staubli *et al.*, Behav., Neural. Biol., 40:58-69, 1984) and olfactory (Staubli *et al.*, Brain Res. 337: 333-336) learning. We have now completed two studies testing the effects of leupeptin on LTP induction. In the first, the drug (20 mg/ml) was chronically infused into the lateral ventricles of rats prepared with chronic stimulation and recording electrodes in the CA1 field. Leupeptin infusion had very little effect on baseline evoked responses but when LTP was tested (3-5 days after beginning infusion) only 3 of 13 animals showed potentiation one day later and only one exhibited stable potentiation for several days. Control animals with saline pumps all (11 of 11) exhibited robust and stable LTP. The block of LTP by leupeptin was reversible: after disconnection of the pumps, LTP was induced in 6 of 7 cases (Staubli *et al.*, 1988). In the second study, hippocampal slices were incubated in the presence of 40-100 uM leupeptin. Incubation for 2 hr or less with the drug had no effect on LTP but after 3 hrs or more, LTP was significantly reduced (Oliver *et al.*, 1989). Examination of the postsynaptic responses to the theta burst stimulation used to induce LTP indicated that leupeptin had no significant effects on the depolarization and presumably the NMDA response in the slices in which LTP was reduced. Studies using recently developed and more selective calpain inhibitors are presently in progress.

It should be noted that neither AP5 nor leupeptin affected acquisition of avoidance conditioning. Current concepts emphasize the existence of multiple memory forms using different brain systems; this may be a reflection of these distinctions.

We have conducted a number of studies examining the nature of the olfactory memory system. As noted above, others have shown that rats acquire learning-sets for odor discriminations and this is dependent on the dorsomedial nucleus of the thalamus. Once the learning-set is formed, rats learn new discriminations after as few as one exposure to each of an odor pair. Training on as many as 30 odor pairs was found not to impair subsequent learning of new pairs, indicating that the capacity of the system is substantial and that already established representations do not interfere with learning of new ones (Staubli *et al.*, 1987). These results are in accord with findings from experiments using the piriform network simulation. Tests using novel odor pairs composed of smell mixtures having common component odorants indicated that rats learn these as gestalts rather than analyzing the components, also in agreement with the simulation. However, when a previously-learned odor was included in a composite odor of reversed valence, rats were impaired as if they were perceiving the known smell rather than a novel one (Staubli *et al.*, 1987). This result also has an analog in the model.

Influence of the hippocampus on olfactory learning was tested by removing its primary input, the entorhinal cortex. Entorhinal lesions resulted in rapid forgetting of olfactory discriminations - that is, a discrimination was acquired normally during a training session, but no significant retention was displayed 3 hrs later (Staubli *et al.*, 1986). These results imply that a system activated by the hippocampus, perhaps involving the medial septum-diagonal bands complex, is necessary for long-term retention.

PUBLICATIONS

1. Staubli, U., Fraser, D., Kessler, M. and Lynch, G. Studies on retrograde and anterograde amnesia of olfactory memory after denervation of the hippocampus by entorhinal cortex lesions. *Behav Neural Biol* 45:432-444, 1986.
2. Staubli, U., Fraser, D., Faraday, R. and Lynch, G. Olfaction and the "data" memory system in rats. *Behav Neurosci* 101:757-765, 1987.
3. Roman, F., Staubli, U. and Lynch, G. Evidence for synaptic potentiation in a cortical network during learning. *Brain Res* 418:221-226, 1987.
4. Staubli, U. and Lynch, G. Stable hippocampal long-term potentiation elicited by 'theta' pattern stimulation. *Brain Res* 435:227-234, 1987.
5. Larson, J. and Lynch, G. Role of *N*-Methyl-D-Aspartate receptors in the induction of synaptic potentiation by burst stimulation patterned after the hippocampal theta rhythm. *Brain Res* 441:111-118, 1988.
6. Staubli, U., Larson, J., Thibault, O., Baudry, M. and Lynch, G. Chronic administration of a thiol-proteinase inhibitor blocks long-term potentiation of synaptic responses. *Brain Res* 444:153-158, 1988.
7. Lynch, G., Granger, R., Larson, J. and Baudry, M. Cortical encoding of memory: hypotheses derived from analysis and simulation of physiological learning rules in anatomical structures. In: *Neural Connections, Mental Computations* (L Nadel, LA Cooper, P Culicover, RM Harnish, Eds), Cambridge, Bradford Books/MIT Press, 1988, 180-224.
8. Lynch, G. and Larson, J. Rhythmic activity, synaptic changes, and the "how and what" of memory storage in simple cortical networks. In: *Brain Structure, Learning and Memory* (JL Davis, RW Newburgh & EJ Wegman, Eds), Boulder, Colorado, Westview Press, 1988, 33-68.
9. Larson, J. and Lynch, G. Priming, NMDA receptor activation, and LTP induction by theta pattern stimulation. In: *Frontiers in Excitatory Amino Acid Research* (EA Cavalhiero, J Lehmann & L Turski, Eds), New York, Liss, 1988, 411-418.

10. Staubli, U., Thibault, O., DiLorenzo, M. and Lynch, G. Antagonism of NMDA receptors impairs acquisition but not retention of olfactory memory. *Behav Neurosci* 103:54-60, 1989.

11. Lynch, G., Granger, R. and Larson, J. Some possible functions of simple cortical networks suggested by computer modelling. In: *Neural Models of Plasticity: Experimental and Theoretical Approaches* (JH Byrne & WO Berry, Eds), San Diego, Academic Press, 1989, pp 329-362.

12. Granger, R., Ambros-Ingerson, J., and Lynch, G. Derivation of encoding characteristics of layer II cerebral cortex. *J Cog Neurosci* 1:61-87, 1989.

13. Larson, J. and Lynch, G. Theta pattern stimulation and the induction of LTP: The sequence in which synapses are stimulated determines the degree to which they potentiate. *Brain Res* 489:49-58, 1989.

14. Lynch, G., Larson, J., Staubli, U. and Ambros-Ingerson, J. Long-term potentiation and memory operations in cortical networks. In: Perspectives in Cognitive Science (R.G. Lister and H.J. Weingartner, Eds.), Oxford Press: New York (in press)

15. Granger, R., Ambros-Ingerson, J., Staubli, U. and Lynch, G. Memorial operation of multiple, interacting stimulated brain structures. In: *Neuroscience and Connectionist Theory* (M. Gluck and D. Rumelhard, Eds), Hillsdale: Erlbaum Assoc. 1989 (In press).

16. Granger, R., Ambros-Ingerson, J., Henry, H., and Lynch, G. Partitioning of sensory data by a cortical network. *Proceedings of 1st Annual Conference Neural Information Processing Systems*, New York, American Institute of Physics Pub., pp. 317-337, 1989.

17. Granger, R. and Lynch, G. Rapid incremental learning of hierarchically organized stimuli by layer II sensory (olfactory) cortex. In: *Parallel Distributed Processing: Implications for Psychology and Neurobiology* (R.G.M. Morris, Ed), Oxford Univ Press. 1989 (in press)

18. Lynch, G. and Granger, R. Simulation and analysis of a simple cortical network. *Psychol Learning Motiv* (In press.)

19. Staubli, U. and Lynch, G. Stable depression of potentiated synaptic responses in the hippocampus induced by low frequency stimulation. *Brain Res.* (in press)

20. Oliver M.W., Baudry, M., and Lynch, G. The protease inhibitor leupeptin interferes with the development of LTP in hippocampal slices. *Brain Res.* (in press).

21. Greenberg, J., Larson, J., and Lynch, G. Evidence for an LTP refractory period. *Soc. Neurosci. Abstr.* 14 (1988) 566.

22. Larson, J., Jung, M.W., and Lynch, G. Effects of NMDA and non-NMDA receptor antagonists on synaptic transmissiton in piriform cortex. *Soc. Neurosci. Abstr.* 15 (1989) 928.

23. Staubli, U., Larson, J., and Lynch, G. Mossy fiber potentiation involves different substrates than those mediating LTP. (submitted)

24. Jung, M.W., Larson, J., and Lynch, G. Physiology and pharmacology of long-term potentiation in piriform cortex (in prep.).

25. Jung, M.W., Larson, J., and Lynch, G. Effects of DNQX and AP5 on synaptic transmission in piriform cortex (in prep.).

26. Larson, J., Greenberg, J., and Lynch, G. Evidence for an LTP refractory period (in prep.).

27. Granger, R., Ambros-Ingerson, J., Anton, P., Whitson, J.W. and Lynch, G. Computational action and interaction of brain networks. In: *Introduction to neural and electronic networks* (S.F. Zornetzer, J.L. Davis, and C. Lau, Eds.), Academic Press: New York, pp 25-41, 1989.

28. Granger, R., Ambros-Ingerson, J., Whitson, J.W., Staubli, U. and Lynch, G. Clustering computations of brain networks simulations. In: *Connectionism in Perspective* (R. Pfeifer, Z. Schreter, F. Fogelman, L. Steels, Eds.), Elsevier: Amsterdam, pp. 199-212, 1989.

29. Granger, R., Gluck, M.A., and Lynch, G. Neurobiological analogs of basic level processing in primary sensory cortex. (submitted)

30. Granger, R., Whitson, J.W., and Lynch, G. Asymmetry in cortical networks enhances hierarchical clustering. (submitted)

31. Ambros-Ingerson, J., Granger, R., and Lynch, G. Simulation of paleocortex performs hierarchical clustering. (submitted)